REMARKS

Reconsideration and withdrawal of the rejections made in the instant Office Action are respectfully requested, in view of the foregoing amendments and following remarks.

Summary of Specification Amendments

The Specification is amended to delete the recitation "in a culture broth" to more clearly define the present invention. No new matter is added.

The Specification is also amended to define the abbreviations "IFO" and "JCM" and their addresses. No new matter is added.

Summary of Claim Amendments

Claims 1 and 8 are amended to even more particularly claim the subject matter of the invention. Claim 6 is canceled. The subject matter recited in canceled Claim 6 is added to Claim 1.

Clam 1 has been amended to delete the recitation "in a culture", and to include the subject matter recited in canceled Claim 6 to more clearly define the claimed invention. Support for this amendment can be found throughout the specification, in particular in original Claim 6. Therefore, no new matter is added.

Claim 8 has been amended to delete the species *Sphingomonas terrae* IFO15098.

Summary of Office Action

(1) In the Office Action, the Examiner rejects claims 1-9 under 35 U.S.C. § 112 ¶1 in view of the amended claims. Specifically the Examiner rejects these claims because independent claim 1 was amended to delete the phrase "as is well known" and add the phrase "in a culture broth." The Examiner asserts that the specification does not provide support for these amendments. The Examiner also asserts that the amendment made to claim 8 to replace "ATCC

15098" with "IFO 15098" is new matter, because both of these are fungus and *Actinomycestes* (respectively) which have similar properties. Further, the Examiner asserts the names and addresses of the depositories of the claimed strain have not been added to the specification.

(2) The Examiner rejects claims 1-9 under 35 U.S.C. § 112 ¶2 for being indefinite in view of the amendment made to claims 1 and 6. The Examiner asserts that the phrase "show no hyphal growth in a culture broth" in claims 1 and 6 is indefinite and confusing because it is inconsistent with the disclosure of the specification.

(3) The Examiner has removed the rejection of claims 8 and 9 under 35 U.S.C. § 102 or in the alternative §103.

(4) The Examiner maintains the rejection of claims 1-7 under 35 U.S.C. § 102 or in the alternative §103 based on the documents of record. Specifically, claims 8 and 9 are rejected under 35 U.S.C. § 102(a), as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a), as allegedly obvious over each of four documents, i.e.,

(1) WO 99/60151 to Kranjc et al. (corresponding to U.S. Patent No. 6,365,382);
(2) U.S. Patent No. 6,043,064 to Davis et al. (corresponding to Japanese Application No. 7-184670 acknowledged at page 2 of the present application);
(3) U.S. Patent 5,942,423 to Demain et al.; and
(4) Okazaki et al., J. Antibiot. 36: 1176-1183, 1983.

The Examiner has indicated that Claims 8 and 9 contain allowable subject matter.

Rejection of Claims 1-9 under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-9 under 35 U.S.C. § 112 ¶1, as containing subject matter which was not described in the specification is such a way as to reasonably convey to one skilled in the art the relevant art at the time the application was filed, in view of the amended claims. Specifically the Examiner rejects these claims because independent claim 1 was amended to delete the phrase "as is well known" and add the phrase "in a culture broth." The Examiner

asserts that the specification does not provide support for these amendments. The Examiner asserts that the added phrase "in a culture broth" is new matter because neither the generic disclosure nor the examples of the specification provide support for new genuses of microorganisms having the ability to sporulate and show no hyphal growth in a culture. The Examiner also asserts that the amendment made to claim 8 to replace "ATCC 15098" with "IFO 15098" is new matter, because both of these are fungus and *Actinomycestes* (respectively) which have similar properties. Further, the Examiner asserts the names and addresses of the depositories of the claimed strain have not been added to the specification.

In response to this rejection, Applicants have deleted (1) the recitation "in a culture broth" in the specification and in Claim 1; and (2) the specie "*Sphingomanas terrae* IFO15098" in claim 8. Further, Applicants have amended the specification to include the names and addresses of the depositories of the claimed strained, i.e., the names of the abbreviations "IFO" and "JCM" and their addresses. Accordingly, Applicants respectfully submit that this rejection has been overcome.

Rejection of Claim 8 under 35 U.S.C. § 112

Claim 8 is rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which allegedly was not sufficiently described in the specification to be enabled thereby. In particular, the Examiner asserts that the amendment made to claim 8 to replace "ATCC 15098" with "IFO 15098" is new matter, because both of these are fungus and *Actinomycestes* (respectively) which have similar properties. Further, the Examiner asserts the names and addresses of the depositories of the claimed strain have not been added to the specification.

In response to this rejection, Applicants have deleted the specie "*Sphingomanas terrae* IFO15098" in claim 8 as discussed above. A s discussed above, Applicants have amended the

specification to include the names and addresses of the depositories of the claimed strained, i.e., the name of the abbreviations "IFO" and "JCM" and their addresses. Accordingly, Applicants respectfully submit that this rejection has been overcome.

Rejection of Claims 1-9 under 35 U.S.C. § 112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the invention. The Examiner asserts that the phrase "show no hyphal growth in a culture broth" in claims 1 and 6 is indefinite and confusing because it is inconsistent with the disclosure of the specification. The Examiner asserts that the genera, species, and strains of the microorganisms recited in dependent claims 6-9 "would reasonably" show at least some hyphal growth in any media. Therefore, the Examiner concludes the specification discloses microorganisms having the ability to sporulate and grow in hyphal forms, and thus, contradicts the pending claims. The Examiner further asserts that the ability of microorganisms to grow in a culture broth depends on the degrees of contamination and purification of the broth. Thus, the ability of microorganisms to grow in a culture broth depends on the process conditions of the broth which is not part of the claimed invention, and thus renders claims 1-9 indefinite.

In response to this rejection, Applicants have amended Claim 1 to delete the recitation "show no hyphal growth in a culture broth." Accordingly, Applicants respectfully submit that this rejection has been overcome.

Rejection of Claims 1-7 under 35 U.S.C. § 102(a) and 103(a)

The Examiner maintains the rejection of Claims 1-7. Thus, Claims 1-7 are rejected under 35 U.S.C. § 102(a), as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a), as allegedly obvious over each of four documents, i.e.,

(1) WO 99/60151 to Kranjc et al. (corresponding to U.S. Patent No. 6,365,382);

(2) U.S. Patent No. 6,043,064 to Davis et al. (corresponding to Japanese Application No. 7-184670 acknowledged at page 2 of the present application);

(3) U.S. Patent 5,942,423 to Demain et al.; and

(4) Okazaki et al., J. Antibiot. 36: 1176-1183, 1983.

The Examiner is maintaining these rejections because although the Examiner considered the arguments in the Amendment filed February 9, 2004 that there are differences between microorganisms of the art (ATCC 19795, ATCC 35024, *Actinomadura, Nocarda autotrophica*) and the claimed microorganism *Rhodococcus rhodochrous* ATCC 21430, the Examiner asserts that (1) the pending claims are not directed only to *Rhodococcus rhodochrous* ATCC 21430, and (2) the differences between this strain and microorganisms having no ability to sporulate and showing no hyphal growth in a culture broth cannot be easily assessed.

The Office Action does not provide any exaplanation as to why the claimed microorganisms are not patentable

In response to this rejection, Applicants respectfully point out that the Office Action does not provide any explanation as to why the remaining claimed microorganisms (besides the claimed microorganism *Rhodococcus rhodochrous* ATCC 21430) are not patentable over the art microorganisms (i.e., ATCC 19795, ATCC 35024, *Actinomadura*, and *Nocarda autotrophica*). Specifically, the Office Action does not provide any explanation as to why the other claimed microorganisms are considered to be identical to or similar with the art microorganisms.

The Office Action does not provide any response to arguments made by Applicants in the Response filed February 9, 2004

The Office Action also does not provide any response to arguments made by the Applicants in the Response filed February 9, 2004 in view of the August 7, 2003 Office Action.

Specifically, the August 7, 2003 Office Action states that Kranjc et al. teach a process of hydroxylation using a strain of *Amycolatopsis orientalis* ATCC19795. ATCC19795 was deposited as *Streptomyces orientalis*, and other strains of this species are or have been classified as *Norcardia orientalis*. Inasmuch as at least strain ATCC21430 is now classified as *Norcardia sp.* and in view of the inconsistencies and ambiguities in the instant record, it is stated that the process of the present invention is anticipated by the reference. Based on the website of the ATCC, some strains of *Nocardia* are now classified as *Amycolatopsis* and the like.

Further, the Office Action states that even if the claimed microorganism is not identical to the referenced microorganisms with regard to some unidentified characteristics, the differences are considered to be so slight that the referenced microorganisms is likely to possess the same characteristics of the claimed microorganism particularly in view of the similar characteristics which have been shown to share. Thus, the rejection reasons that the claimed process would have been obvious those skilled in the art.

Response filed February 9, 2004 responding to the August 7, 2003 Office Action

In response to the August 7, 2004 Office Action, Applicants argued in the Response filed February 9, 2004 that according to classification manuals known in the art, such as Bergey's Manual (References 4 and 5), the genus is classified according to various chemotaxonomical characteristics. Hence, it is common in the art to determine that DNA-DNA homology value of 20% or less between microorganisms belong to different genus based on various chemotaxonomical characteristics. It is clear that the microorganisms having a homology of

only 20% or less on nucleotide sequence level of DNA cannot share similar property. Therefore, there is no ground for the Examiner's comments that the hydroxylation reaction using microorganisms belonging to *Rhodococcus* is obvious from the disclosure of the cited documents that microorganisms belonging to *Amycolatopsis* has an hydroxylation activity.

Silence to Applicants' arguments made in the Response filed February 9, 2004

Although maintaining the rejection of Claims 1-7, the Office Action does not address Applicants' arguments made in the February 9, 2004 arguments. The Office Action does not provide any explanation as to why Applicants' arguments directed to the patentability of Claims 1-7 are not persuasive. Accordingly, Applicants request that Applicant's arguments made in the February 9, 2004 Response be addressed.

Request for Non-Final Office Action

In view of the concurrent filing of a Request for Continued Examination, Applicants' arguments in response to the previous Office Action, Applicants respectfully submit that either the present claims should be allowed, or the next Office Action should be non-final, so that Applicants have a full and fair opportunity to respond.

Attached dendrogram

In order to advance prosecution of this application, Applicants are attaching hereto a dendrogram illustrating the genetic distance of the art microorganisms and the claimed microorganisms. The attached dendrogram was prepared using MEGA version 2.1 (Sudhir Kumar, Koichiro Tamura, Ingrid B. Jakobsen, and Masatoshi Nei (2001) MEGA2: Molecular Evolutionary Genetics Analysis Software, Arizona State University, Tempe, Arizona, USA) based on the nucleotide sequences of ribosomal DNA's of each strain which are aligned on the Ribosomal Database Project II (http://rdp.cme.msu.edu/html/index.html).

The microorganisms recited in Claim 1 (having the closest genetic distance to each of the art microorganisms) are shown in the table below in relation to the genetic distance of the art microorganisms (calculated as discussed above):

Microorganisms Measured	**Distance (Knuc)**
Rhodococcus and *Amycolatopsis (*Art microorganism *ATCC* 19795*)*	0.080 Knuc
Mycobacterium and *Pseudonocardia (*Art microorganism *ATCC* 35024*)*	0.082 Knuc
Arthrobacter and *Actinomadura (*Art microorganism)	0.102 Knuc
Rhodococcus and *Nocardia (*Art microorganism)	0.065 Knuc
Mycobacterium and *Nocardia (*Art microorganism)	0.065 Knuc

It is known in the art that genetic distance between different species of a same genus is smaller than that between different genera.

As acknowledged by the Examiner, *Amycolatopsis orientalis* (ATTC 19795) of Kranjc or particular strain of *Nocardia* of Okazaki et al. is genetically different from *Rhodococcus rhodochrous* (ATTC 21430); thus the process of the present invention using *Rhodococcus rhodochrous* (ATTC 21430) is novel and unobvious over the cited art.

It is known it the art that the genetic distance between different species of the same genus is smaller than that between different genera. As acknowledged by the Examiner, *Amycolatopsis orientalis* (ATTC 19795) or particular strain of *Nocardia* is a genetically different strain from *Rhodococcus rhodochrous* (ATTC 21430). Thus, one of skill in the art would conclude that even if *Amycolatopsis orientalis* and *Nocardia autotrophica* have a hydroxylation activity, it

would not have been obvious that microorganisms belonging to *Rhodococcus* would have hydroxylation activity with a microorganism of Claim 1.

As shown in the table above, the genus of *Pseudonocardia autotrophica* (ATTC 35024) of Davis et al. document is different from the genus of the strains belonging to *Mycobacterium gilvum* of Claim 1 even though it has the closest genetic distance to *Pseudonocardia autotrophica* (ATTC 35024) of Davis et al. The genetic distance of these two microorganisms of 0.082 Knuc is longer than the genetic distance of 0.080 Knuc between Am*ycolatopsis orientalis* (ATTC19795) of the art and *Rhodococcus rhodochrous* (ATCC 21430) of Claim 1. Therefore, even if *Pseudonocardia autotrophica* (ATTC 35024) of the art has the ability of hydroxylating a particular microorganism, it would not have been obvious to a skilled artisan that microorganisms belonging to *Mycobacterium* would have the ability of hydroxylating a microorganism of Claim 1.

Similarly, the genus belonging to *Actinomadura* of Demain et al. is different from the genus belonging to *Arthrobacter ramosus* of Claim 1 (even though it has the closest genetic distance to *Actinomadura*). As shown in the table above, the genetic distance between *Actinomadura* and *Arthrobacter* of 0.102 Knuc is longer than the genetic distance of 0.081 Knuc between *Amycolatopsis orientalis* (ATTC 19795) and *Rhodococcus rhodochrous*. Since the Office Action acknowledges that *Amycolatopsis orientalis* (ATTC 19795) and *Rhodococcus rhodochrous* are genetically different strains, it is clear to one of skill in the art that strains belonging to *Actinomadura* and *Arthrobacter* are also genetically different strains. Hence, even if a particular strain of *Actinomadura* has the ability to hydroxylate a particular microorganism, it would not have been obvious to a skilled artisan that microorganisms belonging to *Arthrobacter* would have the ability of hydroxylating a microorganism of Claim 1.

Further, the genus belonging to *Nocardia autotrophica* of Okazaki et al. is different from the genus belonging to *Mycobacterium gilvum* of Claim 1 (even though it has the closest genetic distance to *Nocardia*). As shown in the table above, the genetic distance between *Nocardia autotrophica* and *Mycobacterium* of 0.065 Knuc is the same as the genetic distance of 0.065 Knuc between *Nocardia autotrophica* and *Rhodococcus rhodochrous*. Since the Office Action acknowledges that *Nocardia autotrophica* and *Mycobacterium gilvum* are genetically different strains, it is clear to one of skill in the art that strains belonging to *Nocardia autotrophica* and *Arthrobacter* are also genetically different strains. Hence, even if particular strain of *Nocardia autotrophica* has the ability to hydroxylate a particular microorganism, it would not have been obvious to a skilled artisan that microorganisms belonging to *Mycobacterium* would have the ability of hydroxylating a microorganism of Claim 1.

In sum, even if the strains of each of the cited documents have the ability to hydroxylate a particular microorganism, it is not obvious that the microorganisms of Claim 1, having the closest genetic distance to each of the strains of the cited documents, would not have the ability to hydroxylate with the microorganisms of Claim 1. Hence it would also not be obvious to one skill in the art that microorganisms belonging to other genera recited in Claim 1, which have longer genetic distance to each of the strains of the cited documents, would have the ability to hydroxylate with a microorganism of Claim 1.

Further, as argued in the Response of February 9, 2004, according to classification textbooks, such as BERGEY'S MANUAL, a genus is classified according to various chemotaxonomical characteristics. Thus, it is common in the art to determine that DNA-DNA homology value of 20% or less between microorganisms belong to different genus based on various chemotaxonomical characteristics. It is clear that the microorganisms having a

homology of only 20% or less on nucleotide sequence level of DNA cannot share similar property. Therefore, there is no ground for the Examiner's comments that the hydroxylation reaction using microorganisms belonging to *Rhodococcus* is obvious from the disclosure of the cited documents that microorganisms belonging to *Amycolatopsis* has an hydroxylation activity.

Accordingly, Applicants respectfully submit that there is nothing in the cited documents, either alone or in combination thereof, teaches or suggests the claimed invention.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the forgoing rejections.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. Applicants also request that in the event of a Notice of Allowance is not issued, that a Non-Final Office Action be issued.

If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to telephone the undersigned at the telephone number below.

Respectfully submitted,
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October 14, 2004
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